Case #	Disease	Mutation/Deficiency	Inheritence	Effects
1	X-linked Agammaglobulinemia	**Deficiency in Bruton's Tyrosine Kinase**	**X-linked**	X-linked so usually in males. VERY FEW B lymphocytes. Pt has no tonsils (tonsils are purely B cells). So patient has no antibodies and are at risk for infections with Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, and Staphylococcus aureus. Intracellular pathogens (as well as common viral diseases) can be killed by cell mediated immunity so these infections can be cleared. T cell number and function are normal. Antibodies are important for neutralization of toxins and viruses, and binding to bacteria to cause opsonization (e.g. the Fc portion of IgG flag a bacterium for uptake by macrophages via an Fc receptor or cause MAC formation and lyses of cells). Tx: dose of gamma globulin intravenously to maintain IgG levels (needs to disaggregated or it will cause immune complexes to form). Cause: Bruton's tyrosine kinase (Btk) deficiency, which acts in B cell maturation. Btk is a tyrosine kinase. Btk is found in pre-B cells, B cells, and PMN. Btk is required to mediate the survival and further differentiation of the progenitor B cells in which successful rearrangement of their heavy-chain genes has occurred. Also needed for the survival of mature B cells. In women that carry the Btk mutation X inactivation is not random b/c if you have a Btk mutation in a chromosome you wont get a functional BCR so the other Btk on the other chromosome will be activated to try to make a function Btk which it will. Dont give live vaccines to XLA patients b/c they cant neutralize the vaccine and after time the viruses can revertant and disseminate through the bloodstream and infect cells. Dx: B cells have CD19 and all T cells have CD3
2	X-Linked Hyper IgM Syndrome	**Mutation in CD40L**	**X-linked**	X-linked. Mutation in CD40L. CD40L stabilized interactions of T cells with B cells and APCs (all APC's have CD40). Patients with deficiency in CD40L= Reduced levels of antibodies, Lack of isotype switching, reduction in cell mediated immunity (No activation of macrophages or CTL or NK cells) PYOGENIC (lack of isotype switching to better opsonizing Ig's) and OPPORTUNISTIC infections (cell mediated immunity is compromised--example Pneumonocytis carinii). CD40L:CD40 interaction in T and B cells causing IL-4 secretion by T cells which induces B cells to make IgE. IL-13 can also cause switching to IgE.NO CD40L:CD40 interaction = ONLY IGM. B/c no interaction of T cells and APCs means no prolif of T cells which means you will find a low number of them in these patients. These patients STILL CAN MAKE ABs!-->via the T independent pathways of B cell stimulation!. TI-1= B cell binds to an antigen and receives secondary activation by toll like receptors.; TI-2 is when the antigen is a molecule with multiple repeating subunits which can simultaneously cross link enough B cell receptors to fully activate the B cells. TI-2 Ags can induce both Igm and some class switched responses.
3	Activate-induced Cytidine Deaminase (AID) Deficiency	**Deficiency in AID (SMH and isotype switching)**	**Autosomal Recessive**	Autosomal Recessive. Lack of isotype switching and no affinity maturation (caused by somatic hypermutation)<--both happen only in B cells. Can also occur with mutation in uracil-DNA glycosylase (UNG). AID removes amino group from C base turning it into U (not normally in DNA so recognized by UNG and removes the U base). No class switching leads to Hyper IgM syndrome. PYOGENIC INFECTIONS ONLY because CD40 is functional allowing T cells to interact just fine with APC's (T cells don't SMH or isotype switching so cell mediated immunity is usually fine. Pyogenic bacteria are resistant to destruction by phagocytic cells unless they are opsonized (in healthy ppl IgM switching to a better opsonizing like IgG1) so ppl with lots of IgM can't make better opsonizing Igs. Also germinal center DO form w/in L.N. because they still have normal CD40:CD40L interaction. Important bacteria--> H. influenza, Strep pneumo, Strep pyogenes, S. aureus
4	Common Variable Immunodeficiency	**Mutation in BAFF or APRIL or receptor TACI**		Mutation in BAFF or APRIL or receptor TACI (autosomal dominant inheritence). BAFF and APRIL induce class switching to IgA and IgG in the presense of TNF-b or IL-10 and induce IgE in the presense of IL-4. BAFF and APRIL bind TACI (this mediates isotype switching)Marked by low levels of IgA, IgG and IgE, Respiratory and GI infections (b/c decrease in IgA and IgG). Enhanced risk of autoimmune diseases (mostly blood related), lymphomas and gastric carcinoma. TI-1 (LPS) directly induces B cell division B cell binds to an antigen and receives secondary activation by TLR4; TI-1 Ags are INEFFICIENT inducers of affinity maturation and memory B cells TI-2 is when the antigen is a molecule with multiple repeating subunits which can simultaneously cross link enough B cell receptors to fully activate the B cell. TI-2 Ags can induce both Igm and some class switched responses.
5	X-linked Severe Combined Immunodeficiency	**Mutations in the gene encoding the common gamma chain (γc) of many IL-Rs**		Any dysfunction in functional T cells will lead to SCID, which presents with normal B cells and lack of T cells. (But need T cells for functional B cells so it is combined) Jak-3 is a protein needed to transduce a signal from the IL receptors with the common gamma chain). Defects in the γc chain (gamma common) of IL receptors will also cause T-B+NK- SCID. Tx: Bone marrow transplant to reconsistute immune function but mature T cells in the bone marrow graft need to be removed b/c they can cause graft-vs.-host dz. DO NOT give live vaccine
6	Adenosine Deaminase Deficiency	**Deficiency of ADA (also seen in PNP def)**		ADA normally degrades adenosine and deoxyadenosine into inosine (and deoxy) and to urate. No ADA leads to increased dATP which inhibits ribonucleotide reductase used in synthesis of all deoxynucleotides. Thymus contains 14 x's more ADA than any other tissue. ADA def leads to deficiency of 5' nucleotidase in T and B cells which usually degrates AMP and dAMP to prevent excessive accumulation of toxic metabolites. Failure of this pathway leads to toxic levels in both B cells and T cells (NO B OR T CELLS BUT NORMAL NK CELLS). T-B-NK+ SCID results. Defects in purine nucleoside phosphorylase (PNP) can cause the same effects. NEVER GIVE SCID PATIENTS A LIVE VACCINE

7	Omenn Syndrome	**Partial missense mutation in RAG1 or RAG 2**	**Autosomal Recessive**	Autosomal Recessive. Partial mutation in RAG genes causing partial enzymatic activity. (Full mutation would be SCID). RAG enzymes are involved in recombination during B cell and T cell development. Partial mutation in RAG lead to development of VERY RESTRICTED repertoire of Ag specificities in TCR and BCR. These few Ag receptors are inadequate for protection and babies develop SCID. Babies need bone marrow transplant b/c thats where lymphocytes are made and in this syndrome lymphocytes are not properly produced. Sx: Eosinophilia, elevated IgE (this is b/c there are few T cell made and must be Th2 (TH0-->Th2 via IL-4 from APC). Th2 secrete IL4 (needed for IgE switching and mast cells), and IL5 (recruit eosinophils) lack of B cells (the few that were there class switched to IgE b/c of IL-4), and few T cells that are oligoclonal. NEVER GIVE SCID PATIENTS A LIVE VACCINE--b/c they are extremely immuno compromised and wont mount proper response for immunity
8	MHC Class II Deficiency	**Deficiency of MHC II**		CD4 Th1--> activate macros, inflammation and phagocytosis and release TNF-a, IFN-g, and IL-2. CD4 Th2-->located in secdary lymphoid organs which puts them in proximity to stimulate B cells, they secrete IL-4, IL-5, IL-10, and IL-13. The MHC II molecules HLA-DP, DQ, and DR are highly polymorphic and present to CD4 cells and HLA-DO and DM help regulate peptide loading onto MHC II *lack of any of the HLA molecules leads to MHC II Deficiency. MHC II are on APC's (expression can be induced by IFN-g). If you have an infection with an opportunistic infection like Pneumocystis pneumonia you consider a deficiency in T-cell mediated immunity. Lack of CD4 cells b/c no interaction during development with MHC class II molecules. Normal T cell function with the existing T cells (but low number). MHC II molecules present extracellular antigens to CD4 T cells so without this interaction toxins and many bacteria will not be killed or inactivated. Mild SCID. Recurrent Infections. Bone Marrow Transplantation can reconstitute some immune function but not all.
9	DiGeroge Syndrome	**Most common cause is mutation in Tbx1 on chromosome 22q11.2**		Clinical Features: pt with low set ears, downturned eyes, widened area below nasal bridge, small mouth and undersized lower jaw (micrognathia), cleft palate, feeding difficulties, rapid breathing, increased fatigue, bluish discoloration of the skin. Tbx1 is needed for expression of several GF's and TF's important for dev of the thymus (endoderm of 3rd pharyngeal pouch) and parathryoid glands (3rd and 4th pharyngeal pouch) and is also needed to growth, proper alignment and septation of cardiac outflow tract. DiGeorge is characterized by congential heart defects (truncus arteriosus, tetrology of fallot, interrupted aortic arch, or aberrant R subclavian), hypoparathyroidism and hypocalcemia (because of low parathryoid hormone), variable degree of immunodeficiency. Most patients have incomplete DiGeorge syndrome-- small thymus and milder immune defects (decreased T cells but intact T cell function). Severe T cell lymphopenia b/c of no thymic tissue is seen in Complete DiGeorge Syndrome. All degrees of DiGeorge Syndrome are likely to develop Autoimmunity esp leading to a reduction in RBC (even after a successful thymic transplant--need IVIg's for this). Autoimmunity is likely to result from reduced expression of AIRE and survival of autoreactive T cells and Thymus generates regulatory T cells which helps kill autoreactive cells. Tx: thymic transplant (dont need HLA match b/c DC's from host can go to thymus and mediate the positive selection of newly generated thrymocytes) with possible bone marrow transplant after thymic transplant. Bone marrow transplant doesnt generate new T-cell just expands the ones within the graft.
11	Graft vs. Host Disease	**Type IV Hypersensitivity**		Acute: <100 days after transplant; Chronic: >100 days after transplant. Unlike normal organ rejection, GVHD results from the DONOR T-cells (the graft of bone marrow) attacking the RECIPIENT tissue systemically. It generally presents with a rash all over the body including palms and soles (systemic inflammation) beginning on face and neck and goes to trunk, then GI involvement after skin manifestations-->profuse watery diarrhea. This type of reaction only occurs in bone marrow transplants. It is especially hard to match people for this since even if you are perfectly matched at MHC I and II, the minor histocompatibility complexes come into play and are extremely unlikely to be matched in anyone but identical twins. IFNg production by CD4 T cells prolongs and increases GVHD b/c IFNg induces the expression of MHC molecules on cells which makes more targets for donor T cells. Drugs to treat: Prednisolone (corticosteroid), Tacrolimus, and Monoclonal anti T cell Ab's like anti-CD3 or anti-CD2
12	MHC Class I Deficiency	**Deficiency of MHC I**		This disorder can be caused by anything that interferes with the MHC genes, proteins, maturation, peptide loading, etc. MHC I interacts with CD8 T cells which are CTL and MHC I are expressed on every nucleated cell. CTL use FasL and Fas (on target) and MHC I on target interacting with the CTL TCR. FasL:Fas causes transcription of genes and changes that induce apoptosis where as MHC I binding with TCR and other signal induces graules to be release and lyse target cell. TAP 1 and 2 transport peptide fragments generated by the proteasome into ER lumen to be loaded onto MHC I. TAPBP facilitates the interaction of MHC I with TAP 1 and 2 and promotes loading of antigenic peptide on MHC I. Mutations in TAP 1, 2, or TAPBP would effect antigen loading onto MHC 1 which would not allow MHC I to be expressed on the surface which leads to a deficiency in them. If there is a mutation in the MHC I molecule then there will be no DP TCR a:b interacting with MHC I in the thymus to mature into a CD8 T cell but normal CD4. So patients have very low CD8 levels. TCR g:d on the other hand are indep of MHC's so they may form. Delayed type hypersensitivity reactions (Tuberculin test) involves CD4 Th1
13	X-linked Lymphoproliferative Syndrome	**Mutation of SH2S1A**	**X-linked**	SH2 domain containing gene (SH2S1A) encodes a protein SLAM-assoc protein (SAP). SAP interacts w/ cytoplasmic tails of SLAM on T cells and interacts w/ 2B4 on NK cells leading to recruitment of Fyn--> activation of killing machinery-->inhibition of IFN g production. Mutation in SH2S1A results in defective killing by T cells and NK cells, dysregulated cytokine production, uncontrolled lymphocyte prolif. XLP patients may develop B cell lymphomas

14	**Hemophagocytic Lymphohistiocytosis**	**Mutation in ability of CTLs and NK to actually kill targets. Phagocytic destruction of RBC's**		There is both a familial and acquired forms of this disease. Sx: persistent fever, spleen and liver enlargement, increase in WBC in the CSF,severe anemia, thrmbocytopenia, abnormal liver function, and decreased fibrinogen (less clotting). These patients have a continuous activation of NK and CTLs which infiltrate the liver, spleen, bone marrow, and CNS and secrete high amounts of IFN-g. IFN-g activates macros and induces release of IL-6 and TNF-a (proinflammatory cytokines). Phagocytic destruction of RBCs is a result of macrophage activation (NK and CTL's are unable to clear the infection because there are defects on the docking mechanism or priming of lytic granules).Activated macrophages often engluf RBC, myeloid cells, lymphoid cells and platelets-->all of these lead to bone marrow hypoplasi. NK and CTL can recognize the Ag's on the MHC I which cause CTLs to activate and proliferate and secrete large amounts of IFN-g which continuously causes macrophages to release IL-6 and TNF-a (proinflammatory cytokines). Enlarged liver and spleen is b/c of the accumulation of macrophages and increased proliferation of CD8 T cells.
15	Chediak-Higashi Syndrome (CHS)	**Nonsense or null mutation in CHS1 (LYST--lysosomal tracking regulator)**	**Autosomal Recessive**	Autosomal recessive. Have defect in intracellular vesicle trafficking--big issues with innate immunity (can't form phagolysosome). PMN less migratory capacity--accumulation of granules . Adaptive immune problems--NK and CTLs can secrete granules. Recurrent bacterial infections, oculocutaneous albinism, increased bleeding due to platelet dysfunction, in adolescents--CNS disorders--cerebellar ataxis, CNS atrophy, seizures, perpehral neuropthy, cognitive defects, also get accelerated phase (usually after an infection with EBV) of uncontrolled lymphocyte prolif and lymphohistiocytic infiltration char. by fever, lympadenopathy, hepatosplenomegaly, pancytopenia (reduction of platelets, WBC and RBC usually lethal). Dx: giant cytoplasmic genules in WBC and platelets which stains positive with meloperoxidase, decr. PMN, look at hair shaft and see clumps of pigment. NBT tests are normal this measures capacity of a lysosomes to produce ROS through NADPH Oxidate which is intact and functional in CHS patients. Tx: prophylaxis Antibitoics, Bone marrow transplant--doesnt help oculocut. albinism or CNS defects
16	Wiskott-aldrich Syndrome	**Mutation in WAS protein**	**X-linked**	X-linked. Is expressed in WBC & megakaryocytes. T cell's cortical actin cytoskeleton becomes reorganized when a T lymphocytes interacts with other cells through surface receptors. Pts w/ WASP haven an impairment of T-cell actin reorganization. Seen in affected cells & most activities of T cells including cell interactions involving cell attachment where actin is reorganized are affected Ex: cell targeting by CD8 CTLs, and interaction of CD4 cells w/ B cells (CD40L on the T binding to CD40 on B leads to reorganization & local release of cytokines to B cells--so B cells are less rxtive to Ag. Defects in both humoral & T-cell mediated immunity (especially viral infections where CD8 cells would be needed) are found in WAS. Get many infections as well as opportunistic infections Classic WAS triad: repeated infections, eczema, thrombocytopenia w/ small platelets
17	**Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy**	**Mutated AIRE gene**	**Autosomal Recessive**	Autosomal Recessive and high incidence among Finns, Sardinians, and Iranian Jews. This allows for antibodies specific for certain organs (in this case, endocrine, to have auto-reactive antibodies formed against them. Lack of negative selection on T-cells. Autoimmune attack can take several forms. (will see all sorts of autoimmune disorders like Hashimoto's (hypothyroidism), Grave's hyperthryoidism, can also make Antibodies to cytokines (some of which are needed in destroying bacterial infections like candiadasis)
18	Immune Dysregulation, Polyendocrinopathy, Enteropathy X-linked Disease (IPEX)	**Mutation in FoxP3 on T reg cells**		Peripheral tolerance include suppression of autorxt cells by reg T cells (to suppress T cells that escaped central tolerance/negative selection). Mutation in FoxP3 result in loss of function of T reg cells and uninhib T cell activation. T regs release IL-10 which is immunosuppressive and TGF-b which is anti proliferative factor and can induce apoptosis. IPEX results in uncontrolled inflamm at various sites in the body. Common sx: intractable watery diarrhea-->failure to thrive, dermatitis & autoimmune DM development in infancy. Diarrhea is b/c of inflamm in the glut resulting in villous atrophy--> decr absorption--> watery diarrhea. Patient can see other autoimmune diseases and frequent infections (sepsis, meningitis, pneumonia). See elevated IgE but other Ig's are normal. Tx: control inflamm and BM transplant w/ functional T regs for permanent control
19	Autoimmune Lymphoproliferative Syndrome (ALPS)	**Defect in Fas/FasL**	**most are heterozygous for dominant mutation in Fas gene. but other mutations can cause ALPs: FasL, Caspase 10, GOF mutation in NRAS**	Fas binding to FasL brings the death domains in the Fas cytoplasmic tails together. FADD's death domain binds to death domains of Fas and then interacts through a second death domain w/ protease caspase 8. This results in cleaving caspase 8 to release an active caspase domain that can in turn activate other caspases. Ultimately activation of capase activatable DNase (CAD) which is present in all cells in an inactive cytoplasmic form bound to an inhibitory protein called I-CAD. Caspases break down I-CAD and CAD can enter nucleus --> fragment DNA--> apoptosis. Fas and FasL are upreg on lymphocytes during clonal expansion. Patients with ALPS have defective T cell apoptosis and ban accumulation of CD3+ Double Negative (DN) T cells. When B cells are activated (they also express Fas) and become susceptible to Fas-med-apop so activated B cells in ALPS are not properly elim--> serum conc of Ig's increase (hypergammaglobulinemia) as well as the number of B cells and pathological autoAb production ensues (often dev hemolytic anemia, neutropenia, thrombocytopenia, and hepatitis). Also cuz B and T cells are elim properly--> develop lymphomas, LN enlargement, hypergammaglobulinema. Autoimmunity is caused b/c Fas-med killing is mechanism for removing autoAb B cells
20	Hyper IgE Syndrome (Jobs Dz)	**Mutation in STAT-3**	**Autosomal Dominant or Recessive**	Autosomal Dominant or Recessive. IL-12 induced Th1. IL-4 induces Th2. IL-2 and TGF-b induce T regulatory (which have CD25 and FoxP3) IL-21, 6, 1b, TGF-b induce Th17 (RORgT). Th17 act on skin to induce the production of antimicrobial defensins and on endothelial cells to induce the production of chemokines that recruit PMN to sites of infections. Th17 are involved in bacteria defense and autoimmunity. Th17 produces IL-17, IL-22 and IFN-g. Hyper IgE is thought to be caused by decreased neutrophil chemotaxis due to decreased IFN-g. STAT 3 normally activates ROR-gT which is a TF associated with forming Th17 cells. Mutations in STAT3 lead to decrease in Th17 so decrease in IFN-g production --> decrease PMN chemotaxi . Disease presentation--recurrent staph infections, eczema like skin rashes, severe lung infections and very high IgE levels in blood. Autosomal dominant patients have problems with their bones and have two sets of teeth.

21	Ataxia Telangiectasia	**Compound heterozygotes for two different ATM mutations (one mutation in one ATM allele and a different mutation in the other allele). --most common**	**Autosomal Recessive**	DNA damage can be repaired by 2 mechanisms—non homologous end joining (NHEJ) or homologous recombination repair. NHEJ can join DNA ends w/ little sequence homology and can occur in G0, G1, and M phases. Homologous recombination occurs only during the S and G2. DNA ds breaks begins with recruitment of the MRN complex to the site of the break. The MRN facilitates the accumulation of addition proteins like ATM (ataxia telangiectasia mutated—a serine/threonine kinase). ATM exists as an inactive dimer constitutively bound to a phosphatase that negatively regulates ATM kinase activity. ATM binds dsDNA breaks the phosphatase is released--> undergoes autophosphorylation and dissociation into the active monomers--> phosphorylates a large number of downstream proteins involved in DNA repai-->Artemis (a nuclease that processes free DNA ends in prep for ligation) or the MRN complex itself, is important in HR repair-->Activation of these results in cell cycle arrest & DNA repair, or in apoptosis if the DNA cannot be repaired. Redundancy in cellular DNA repair mechanisms permits some DNA repair to occur even in the complete absence of ATM. BUT cells lacking ATM accumulate ds breaks over time, which manifested as an abnormal sensitivity of cells to ionizing radiation and the accumulation of chromosomal abnormalities. Also some parts of the NHEJ pathway are involved in the recombination of Ig's and TCR genes. NHEJ is also thought to be the means by which the ds breaks made in the Ig C region during class switch recombination are resolved. Ataxia telangiectasia is characterized by progressive cerebellar ataxia (earliest sign--usually 2-3 years old), and neurodegeneration, oculocutaneous telangiectasias, primary immunodeficiency, and sensitivity to ionizing radiation. The combination of ataxia with telangiectasias on the conjunctivae or pinnae is characteristic of ataxia telangiectasia. Another identifying feature of the disease is the elevated AFP level. The loss of class switch causes the accumulation of IgM and absense of other Ig's but patients with ataxia telangiectasia are not typically at increased risk of opportunistic infections. Patients with this have an increased risk of leukemia and other cancers. Translocations juxtaposing an active T-cell enhancer in the TCR locus with an oncogene offer a growth advantage to these abnormal cells, resulting in clonal expansion. The defective repair of double-strand breaks caused by ionizing radiation is the primary cause of tumors in those patients
22	Warts, Hypogammaglobulinemia, Infections and Myelokathexis (WBC retention) syndrome	**mutation in CXCR4--heterozygous mutation leading to truncated CXCR4 protein**		CXCR4 is a GPCR and when CXCL12 binds it causes chemotaxis that traffics the cells to a desired location within the organism. CXCL12 is key chemokine that direct the homing of both precursor and muture leukocytes in BM--it binds to the CXCR4 receptor expressed by leukocytes. CXCR4 is found at higher levels on surfaces of immature myeloid progenitors and senescent PMN compares to mature leukocytes. The more receptor on the surface-->the more CXCR12 can cause homing of these cells . CXCL12 is made by BM stromal cells causing the retention of immature myeloid progenitors in BM as well as the elimination of senescent PMN from the periph by homing them to the BM to make them undergo apoptosis. Mutant CXCR4 is synthesized and expressed at the cell surface and is ale to form homodimers or heretodimer w/ normal CXCR4. These dimers maintain the ability to deliver intracellular activating signals but are refractory to beta-arrestin del endocytosis (downreg of the receptor at the cell surface as a response to continuous signaling)--> results in incr chemokine receptor signaling and therefore an incr chemotactic response to CXCL12. Characteristic Sx: peripheral leukopenia (esp PMN), hypercellularity in BM due to an expansion of mature and apoptotic PMN. PYOGENIC INFECTIONS. Hypogammaglobulinemia is freq, also freq dev persistent, treatment-refractory warts results from infection by HPV--defect in trafficking of effector cells (T and NK) and APC's. WHIM patients have abnormal vulnerability to viruses affecting the skin
24	Interferon-γ Receptor Deficiency	**Deficiency of IFN-γR**		When macros phagocytosize they release IL-12--> IL-12 induces TH0 to turn into Th1 and suppress Th2 diff as well as cause Th1 & NK cells to secrete IFNγ-->IFNγ binds to the IFNγR1 which then associates with IFNγR2 when is binds a dimer of IFNγ. IFNγ R1 and R2 are associated with Jak1 and Jak2. the IFNγ receptors must bind a dimer, then the Jak's can combine and activate the JAK-STAT gene transcription cascade. Failure of this pathway leads to increased OPPORTUNISTIC INFECTIONS. E.g. susceptibility to mycobacteria (Tb and avium), Listeria, Leishmania, Salmonella, etc all take up residence in macrophages so they are protected from most immune response. These are only eliminated when their host macrophage is activated and produce increased amts of NO, oxygen radicals and other microbicidal molecules (cant do this w/o IFN-gR (macrophages cannot be activated). **also seen pts with any defects in activation of the JAK-STAT pathway--> defects in p40 subunit of IL-12 (and IL-23), defects in beta1 chain of IL-12R, mutations in STAT1 and NEMO (controls production of IL-12 from macrophage). Patients who have defect in IL-12 or IL-12R are susceptible to BCG (live attenuated Tb vaccine used in Europe) b/c proper immune response cant be mounted because no IL-12 means less Th1 cells and less IFN-g being made to stimulate macrophages to kill. Same thing happens in patients with SCID except they dont have sufficient B or T cells to mount an immune response.
25	Severe Congenital Neutropenia	**Mutation in G-CSF receptor that normally causes myeloid cells to develop into neutrophils**		Mutation causes severe and recurrent bacterial infections involving skin, the umbilical stump, soft tissues, lungs, deep organs or sepsis especially in the first few months of life. Reduced neutrophils (severe is <500 cell per microliter). Can be caused by a lot of things but most talked about by a problem with G-CSF receptor that normally causes myeloid cells to develop into neutrophils. Bone marrow maturation arrests at the promyelocyte stage. If Neutropenia is due to peripheral destruction of neutrophils then bone marrow's ability to make neutrophils is okay (check with bone marrow aspirate). Neutropenia due to decr. production affecting cells at all stages of diff or it may affect more mature myeloid cells only (more mature myeloid cell problems is seen in SCN). Dont give PMN transfusions to treat b/c PMNs are turned over so rapid so all will die within a die and there are risks associated with the transfusion (only use transfusions for severe numerical or functional defects in PMNs (SCN & CGD). If you have somatic mutations makes the G-CSF receptor more active in signaling and cellular hyperactivation thus contributing to the formation of leukemia.

26	Chronic Granulomatous Disease	**Mutation of NADPH oxidase**	**X-linked or Autosomal**	Failure of activated neutrophils to reduce nitroblue tetrazolium (NBT) is a marker of CGD. In people who have CGD but are not due to X-linked mutations (i.e. heterozygous), show a partial ability to still withstand some opportunistic infections. Most are X linked and associated with gp91 mutations (a subunit of NADPH oxidase). When tested with NBT, half the neutrophils have reduced NBT and half do not stain (random X inactivation). Patients with the X-linked mutation have many infections due to the failure of the oxidative burst within the phagocytes –Especially PYOGENIC, Aspergillus. Streptococci, make hydrogen peroxide but doesnt have catalase and is normally killed by reactive oxygen species generated by NADPH Oxidase, but b/c it makes hydrogen peroxide it will kill itself so these patients are not at increased risk for Strep infections. Serratia osteomyelitis is suggestive of CGD.
27	Leukocyte Adhesion Deficiency	**Lack of LFA-1 or Mac-1 Integrins, Lack of CD18 (common β2 integrin chain) for Dr. Takashima.**		T cells have CD3, CD4 and CD8 markers. B cells have CD19, and NK have CD16. Leukocytes perform most of their functions in extravascular sites and ppl with LAD their WBC's cannot extravasate into periphery. E selectin on BV and sialyl-lewis moiety (carb ligand) on WBC bind--> WBC rolls along the BV until LFA-1 and Mac-1 on WBC interacts strongly with ICAM-1 (this is mediated by chemokine-CXCL8)-->Interaction between CD31 on both WBC and BV junctions contributes to diapedesis-->WBC migrates along gradient of CXCL8 secreted by cells at the site of infection. This process also occurs in lymphocytes entering secondary lymphoid tissues via HEV (instead of BV) and uses L-selectin interacting with HEV mucin-like addressins. CD18 is a component of B2 integrins and leads to lack of recruitment of WBC into tissues (so higher than normal WBC in blood) and high susceptibility to multiple bacterial infections including pyogenic (b/c of CR3 mediated uptake of opsonized bacteria by PMN). People with LAD have severe gingivits and very poor wound healing (delayed separation of the umbilical cord is the earliest manifestion) Rebuck skin window test-->measure migration of immune cells into damaged skin.
28	Recurrent Herpes Simplex Encephalitis	**MyD88 def, TLR-3, UNC93B (the protein essential for signaling from TLR-3,7,8 & 9), & TRAF3**	**Mendelian inheritance**	Problem with Type I interferon (IFN-a and IFN-b) signaling leads to recurrent herpes encephalitis due to the brain's inability to clear the infection due to TLR-3 dependent mechanisms and other ones IFNα and IFNβ transcription is induced by Toll-like receptors TLR-3/9 that all recognize dsRNA. TLR 7/8--ssRNA. These TLRs are on PM & endosomes. TLR req assoc w/ endosomal membrane protein UNC93B for signaling. TLR-3 signals through TRIF-->TBK1 and IKKe-->IRF3/7. TLR 7/8/9 signal through MyD88 and IRAK4/1-->activates IKKa:b:g --> activate NFkB--> activates IRF-7. These trigger the interferon production. After type I IFN's are released from virus infected cell--> bind to common receptor a heterodimer of IFNαRI & IFNαR2 on the cell surface.-->activates JAK1 and TYK2 kinases of TF ISGF3--> ISGF3 binds ISRE on promotor for IFN genes-->transcription of antiviral cytokines-->destorys virus. SO HSV-1 can be transported through sensory neurons to trigeminal nerves and ganglia where it set a latent infection. Reactivation--> can invade brain through olfactory tract, and trigem nerves--> infects neuronal and glial cells --> predilection for parietal and temporal lobes; Susceptible ppl---MyD88 def, TLR3 def (limited to CNS phenotype b/c redundancy for systemic control of viral infection), defects in STAT-1 (promotes transcription of IFNg) MyD88 def and IRAK4--incr risk for pyogenic infection but not recurrent HSE
29	Interleukin 1 Receptor Associated Kinase 4 Deficiency (IRAK4 Deficiency)	**IRAK-4 Deficiency**		PAMPs on pathogens interact w/ PRR's on APC's. TLR's are types of PRR and activate NF-kB and upreg proinflamm cytokines like TNFa. TLR's enhance antimicrobial activity of macros, and PMN's and enhance secr of cytokines from macros--> helps attract more WBC's to site of infection. Signaling via TLR's also induce maturation (upreg costim like CD40, B7.1 and B7.2) of DC's and migration to peripheral lymphoid tissues where they activate T cells and produce pro inflam cytokines like TNFa, IL-1, IL-6, and IL-12. They do all this to activate CD4 TH1 cells which then secrete IFN-g. IL-1R and TLR's share a common adaptor protein MyD88, and signal proteins IRAK 1 and 4 and TRAF-6. Successful propagation leads to activation of MAPKs and NFκB transcribing TNFα and IL-6 and IL-12. Functional IRAK-4 is crucial in the ability to make responses to TLR ligands and in its absence signaling via NFkB is blocked. Loss of IRAK-4-->impaired Ab response to polysaccharide Ag's--> recurrent NEISSERIA MENIGITIDIS and STREP PNEUMO infections (both of these have antiphagocytic polysacc capsule and these infections are normally eliminated by opsonizing IgG Abs). PYOGENIC INFECTIONS. No increased susceptibility to viral infections b/c TLR-3/4 can also signal through another pathway via TRIF /TRAM which activated IRF3--> produce Type I IFN's. NORMAL NUMBER OF T AND B CELLS AND NORMAL SERUM IG's and protective Ab titers to protein antigens.
30	**Congenital Asplenia**	**No spleen**		Spleen Red pulp filters and white pulp coats bacteria not phagocytosed in red pulp with antibodies. Spleen has major function in stopping bacterias from disemminating. Adults who lose their spleen have already made antibodies to so many infections so once these migrate into tissues the immune response starts and they are fairly protected. Ppl with asplenia are given immunication to reduce infection with H. influenza and Strep pneumo via IM or SubQ b/c the vaccine will drain in lymph and go to active L.N. Prophylaxis with antibiotics given daily is advised for asplenic patients. To detect a spleen give radioactive colloid gold which is taken up by reticuloendothelial cells in the spleen and liver and then scan for the gold to see if theres a spleen. Susceptibility to bacteremia especially encapsulated bacteria.

31	Hereditary Angioedema	**Deficiency of C1INH**	**Autosomal Dominant**	Autosomal Dominant. C1INH makes sure complement isnt activated when it should be and inhibits C1 (C1 cleaves C2--> C2a --> C2 kinin) Deficient in C1INH normally dissociates C1r and C1s from the active C1 complex. This leads to increase C3a and C4a. In deficient C1INH you have uninhibited activation of Factor XII (cleaves plasminogen-->plasmin which activates C1), which activate vasoactive peptides (bradykinin and C2 kinin. Bradykinin and C2 kinin increase the permeability of the post cappilary venules by causing contraction of the endothelial cells so as to create gaps in the BV wall--> edema). in HANE no effective C3 convertase is formed so mast degranulation seen due to C3a and C5a (noth are anaphylatoxins) is not seen in these patients. B/c no histamine the swelling in HANE does not itch. Sweeling upon minor trauma ↑. HANE patients have a functional alternative pathway (C1INH only works on CP and LP) so they are resistnat to infections. Androgen therapy can increase C1INH by the liver or can use CINRYZE which is pure human C1INH administered i.v.
32	Factor I Deficiency	**Deficiency of Factor I (used in complement)**		Factor I works with Factor H in the alternative pathway to inhibit the alternative C3 convertase and create iC3b, an opsonizer. C3b on host cells is immediately cleaved to iC3b by factor I using coreceptors facotr H, C4BP, CD46 (MCP), or CR1. inactivation of C3b inhibits the formation of convertases (iC3b cannot bind Bb in alternative pathway. This inhibits the activation and amplication of AP on host cells. Small amounts of iC3b cannot activate other complement killing. High levels of iC3b where complement is active and has amplified on nonhost cells acts as an opsonin and binds CR3 and CR4 on phagocytes leading to enhanced phagocytosis. Lack of Factor I leads to enhanced formation of more convertases C3bBb leading to depletion of C3 and factor B. Also leads to Lack of opsonization of bacteria since no iC3b exists and thus bacterial susceptibility. **looks the exact same as factor H deficiency. Patients w/ no H, I or C3 have increased susceptibility to PYOGENIC INFECTIONS (these are killed by opsonization) and disseminated NEISSERIAL INFECTION (cant make MAC on bacterial surface). C3a binds to mast cells and causes mast cell degranulation. C5a is a very strong chemotactic agent for PMNs
33	Deficiency of the C8 complement component	**Deficiency of C8**		Terminal components of complement system aid in formation of MAC complex which forms a pore in the membrane of bacteria leading to cell lysis. CD59 inhibits the action of C8 (insertion into CM) and C9 (component of pore) and prevents formation of MAC on cells of the body but not on bacteria. Incr susceptibility to Neisseria spp. (also occurs in def of properdin and factor D). Use CD50 to measure integrity of all the components of the classical pathway. Def in C1 (q, r, s) and C4 are assoc w/ IC dz b/c of the lack of C4b which is important for attaching to RBC CR1 for removal.
34	Hereditary Periodic Fever Syndromes	**Mutations in genes regulating inflammatory responses**		There are 10 of these. NOMID/CINCA is characterized by excessive IL-1Beta production. IL-1beta causes fever, rash, neutrophilia, thrombocytosis, and production of Acute-Phase Reactants. NOMID/CINCA is a cryopryinopathy. This disease is due to a constitutively active NLRP3 which activates IL-1Beta (and IL-18) by forming the inflammasome complex with protease caspase 1. Summary: Intracellular bacterial infections of macrophages detected by NLRs which is subdivided into NLRPs and NODs. NLRP3 activates IL-1B. In NOMID/CINCA, NLRP3 is constitutively active. IL-1Beta is a pro-inflammatory cytokine that causes fever, rash, neutrophilia, thrombocytosis, and production of acute phase reactants. Also see sensorineural hearing loss in NOMID/CINCA. Treat w/Anakinra (IL-1 receptor antagonist) to down regulate IL-1beta. Colchicine (microtubule inhibitor) and TNFalpha inhibitors also used.
35	**Systemic-Onset Juvenile Idiopathic Arthritis (sJIA)**	**Polymorphisms in the promoters & coding seq. for genes encoding TNF-a, IL-6, and macrophage migration inhibitory factor (MIF) are ASSOCIATED**		TNF-a, IL-1b and IL-6 cause abberant thermoregulation, hematopoesis, tissue inflamm and metabolism. TNF-a (made by macrophages cause anti and pro apoptosis, recruitment of PMN and more macros, and can stim DCs to migrate to L.N. and mature initiating the adaptive immune response). IL-1b (made by macros, monocytes, and DC; increases exp of adhesion molecules on endothelial cells of leukocytes, increase body temp and reg hematopoiesis). IL-6 (produced by T cells and is important for T cell diff and prolif and also diff of B cells into plasma cells. Excess IL-6 causes fever, anorexia, fatigue and elevation os acute phase reactants (CRP, serum amyloid A, and fibrinogen). IL-1b is a zymogen and needs to be cleaved by caspase 1 for activation (proinflamm) and secretion. Caspase 1 is activated by the inflammasome which is activated by multiple things. IL-6 along with TGF-beta indcues the development of Th17 cells. Th17 cells produce IL-17 and TNF-a and also IL-6. IL-17 is a potent mediated of delayed type reactions by increasing chemokine production in various tissues to recruit monocytes and PMN to site of inflamm. Symptoms of sJIA: arthritis,daily high spiking fever for 2 weeks and 1+ of the following: fatigue, rash, enlarged L.N., liver, or spleen, or serositis (inflamm of pleura, pericardium, peritoneum). Labs: elevated TNF-a and IL-6 (mutations prob cause overexpression). DISEASE OF EXCLUSION--need to exlude-->psoriasis in pt or 1st deg relative, arthritis in a HLA-B27 positive male older than 6, Spondyloarthropathy (jt. dz of vertebral column) or acute anterior uveitis (inflamm of iris and ant. chamber) in 1st deg relative, and the presence of IgM rheumatoid factor (Antibody against Fc portion of IgG which join to form immune complexes that contribute to dz process in RA pts) on 2+ occasions at least 3 months apart. No association with autoantibodies in sJIA**

	Rheumatoid Arthritis	**Type III Hypersensitivity**	Unknown trigger sets up initial focus of inflamm in synovial membrane and attract autoreactive WBC's to inflammed tissue. Synovial membrane becomes thickened as a result of hyperplasia and there is an incr. growth of BV's. Rheumatoid arthritis is associated with autoreactive CD4 Th1-mediated inflammatory reaction in joints which activates macrophages and results in the production of TNF-alpha, IL-1, IL-6, IL-17 and IFNg. Cytokines induces MMP's and RANK ligand by fibroblasts--> MMP's attack tissues by activation of bone destroying osteoclasts and cartilage destoying chondrocytes. B cells are activated by binding of CD40 to CD40L and B7.1 to CD28-->activated and secrete Ig's including RF into synovial fluid which activates complement. Several drugs available that interfere with the action of TNFα including ones that trap TNFa in solution such as Etanercept (a soluble form of the TNF receptor) and Infliximab (antibody against TNFα). Others: anakinra (antagonist of IL-1R), tocilizumab (an anti-IL-6R antibody), Rituximab (delete peripheral B cells specifically one's w/ CD20--depletes levels of RF), abatacept (costimulatory molecules inhibitor). RF is an autoab (IgM) that forms IC's. RF is not itself dx of RA. Dx: Stiffness in the joints lasting at least 1 hr (usually symmetrical b/c of synovial inflam), symmetrical arthritis of 3+ joints w/ swelling an/or fluid, rheumatoid nodules, serum RF, typical radiographs. Rheumatoid arthritis occurs less commonly in men than in women and the specific autoantibody in RA is anti-Citrullinated Cyclic Peptide (anti-CCP).
37	Systemic Lupus Erythematosus (SLE)	**Disease nonspecific AutoAb; Type III Hypersensitivity**	C1 (q, r, s) binds soluble immune complexes and lead to activation of C4, 2 and 3. C3b associates with the Ag-containing complex. RBC have CR1 (regulatory protein) which binds to C3b on immune complexes (large ones more easily) which allows the IC to be carried by RBC's to liver and spleen. Macrophages in the liver (Kepffer cells) and spleen remove IgG-containing IC's from RBC surfaces via binding of the Fc regions of the IgG to the Fc-gammaR on the phagocytes. Excessive production of ICs' can overwhelm any residual RBC clearance mech and these soluble complexes tend to become lodged in the walls of small BV's in the kidney glomeruli (causing glomerulonephritis) and the synovial tissues (causing arthritis) of joints causing IC dz (other ex of IC dz--subacute bacterial endocarditis--causes glomerulonephritis, mixed essential cryoglobulinemia--causes systemic vasculitis, and SLE). Clinical features (induced or exacerbated by sun exposure): butterfly rash on cheeks and nose, production of anti-nuclear Ab (ANA) w/ specificity for ds DNA. Progressive SLE is assoc w/ low CH50 and depression in C3 concentration (under these conditions need corticosteroids). More common in WOMEN and more severe in Africans and Asians. AutoAb against dsDNA (specific for SLE), Anti-Smith (specific for SLE) ribronucleoproteins, phospholipid complexes, platelets, and RBC's. ANA can be detected by IF. Will sometimes see false positive syphilis test. Treatment--antimalarials for lupus skin dz.
38	Mixed Essential Cryoglobulinemia	**Cryoglobulins in blood**	Cryoglobulins rep serum Ig complesex that ppt in the cold. These are absent in normal blood. Ppl w/ chronic infections have high levels of Ig's in the blood and persistent immune response to the microbial Ag's can lead to formation of IC's. The IC's can become antigenic and cause IC dz. Cryoglobulinemia is a condition assoc. w/ IC in kidneys (glomerulonephritis--damages ability to remove water and excess fluid from body), BV's (causing vasculitis--in brain or intestines can result in fatal bleeding) and other organs (synovial joints--arthritis). When IC's are deposited on walls of BV's they activate complement--> release C5a which causes WBC infiltration and inflamm in BV wall/vasculitis--> inflamm causes BV to rupture and release blood into skin causing purpura. 40% of ppl with chronic Hep C have this dz caused by production of both polyclonal IgG and monoclonal/polyclonal IgM RF. These RF's bind to Fc on IgG (esp when bound to Ag) and promote IC formation. Tx: reduce circulating B cells (rituximad tx) to reduce Ab production so decr in IC's but rituximad increases the risk of infections esp in HCV (reduced B cells= reduced anti-HCV antibody levels)
39	Crohns Dz	**NOD2 mutation and other ones**	Disorder of mucosal innate immune dysregulation, characterized by inflammatory lesions that can involve the entire GI tract, unlike ulcerative colitis, which involves only the colon and rectum. Inflammatory cell infiltrate is transmural, involves epithelium, lamina propria, and adventitial layers: fistulas and bowel abscesses are common. These are systemic diseases, which can also lead to erythema nodosum, pyoderma gangrenosum, arthritis, and affect the eyes (uveitis). Also an increased risk of GI cancer.Deficiency in NFkB pathway component NEMO or Treg cells leads to IBD. NOD2, intracellular innate immune receptor, expressed in macrophages and epithelial cells, activates production of inflammatory cytokines. NOD2 gene mutation, leads to impaired secretion of antimicrobial peptides (defensins), associated w/ Crohn's. Blau syndrome: autosomal dominant, granulomatous inflammation of eyes, skin, and joints also associated with NOD2 mutations. Other genes assoc. w/ Crohn's: IBD5, IL23R, ATG161L, Chr 5p13.1, Chr 5q33.1 (IRGM), Chr 10q21.1. IL23R required for Th17 cell maintenance. Crohns-->regional enteritis, abd pain, D/V, weight loss, skin rashes, arthritis, NOD2 gene, granulomas. UC--> colitis, colon ulcers, crypt abscesses, diarrhea mixed w/ blood.
40	Multiple Sclerosis	**AutoAb's to myelin Ag's; Type IV hypersensitivity**	T cell are the primary inducers of inflamm. Activated TH1 cells autoreactive for brain Ag's cross BBB and encounter Ag's on microglial cells and secrete cytokines such an IFNg. Production of T cell and macrophage cytokines exacerbates inflame and induces influx of blood cells (macros, DC, and B cells), and blood proteins (complement) into brain. Autoreactive B cells produce autoreactive Ab's against myelin Ag's. Activated mast cells release histamine (more inflamm)--> ultimately leads to demyelination and interference w/ neuronal function. IFNg treatment for MS is CONTRAINDIC. b/c it induces MHC II expression-->enhancing Ag presentation and it drives the differentiation of TH1 cells which are pathogenic for MS. Treatment--corticosteroids (antiinflamm) and cyclophosphamide (cytotoxic); these inhibit T cell prolif and interfere w/ secretion of cytokines that drive inflamm and further T cell activation. Monoclonal Ab natalizumab--block the movement of WBC's from the blood to sites of inflamm. IFNb is also used. Dx: oligoclonal IgG in the CSF b/c only few V cells that enter the CNS have activity for CNS Ag so limited diversity of IgG produced.

41	Autoimmune Hemolytic Anemia	**Autoab's of IgM or IgG class; Type II Hypersensitivity**		HLA-B27 is assoc. w/ autoimmune arthritis occuring after infection by both Chlamydia trachomatis (Reiter's) and enteric pathogens-Shigella, Salmonella typhimurium/enteritidis, Yersinia enterocolitica, Campylobacter -->(all reactive arthritis). Chronic arthritis following Lyme Dz (no response to antibiotics) is strongly assoc w/ HLA-DR2 and 4. Mycoplasma pneumo (atypical pneumo)--> patchy infiltrates in lung; Pneumococcal pneumonia (strep)-->complete opacity and lobar consolidation. Result of infection of mycoplasma pneumo can induce an IgM autoab reactive w/ a branched carb (the I Ag--not fully exp until 6 mo) on RBC's--> anemia b/c of type II hypersensitivity. The IgM autoab binds fairly weakly and agglutination is not seen unless ab's are mised w/ cells in the cold (cold agglutination--agglut in cold and reverse when warm). Paleness in the palms in warm conditions is a sign of anemia. Autoab's are either IgM or IgG and bring about lysis of RBC by complement fixation or adherence of the RBC to the FcR-g on the cells of the fixed mononuclear phagocytes system primarily in the spleen but also in liver and other organs. Direct coombs test (was a question in the case)--antibody designed to detect C3 or C4 on RBC's is aimed at either C3d or C4d b/c the ester that binds to IgM autoAb is in the C3/4d fragments and once the autoab is bound to C3b or C4b it can be digested by Factor I into C3c and C3d and C4c and C4d. C3/4c would be released from the Ag:Ab complex and thus Ab's against them would not agglutinate the RBC's.
42	Myasthenia Gravis	**AutoAb (anti-IgG Ab) against ACh Receptors; Type II hypersensitivity**		Antibodies against ACh Receptors. See fluctuating weakness that worsens w/ activity and improves w/ rest. Pregnant women w/ MG transfer dz to newborn b/c IgG is only Ig that crosses the placenta. Most often first seen in laryngeal / ocular muscles--eyelids are droopy; when gazing R--R eye moves and L eye stays straight; when gazing L--L eye moves and R eye stays straight. CXR of young ppl w/ MG show enlargement of thymus (removal of thymus esp in patients w/ thymoma may improve sx. Tx: Pyridostigmine (ACh esterase inhibitor) and Azathioprine--cytotoxic agent that is immunosupp.
43	Pemphigus Vulgaris	**Autoimmune against desmoglein; Type II hypersensitivity**	**Commonly seen in Ashkenazi Jews who have certain HLA type (HLA-DR4--an MHC II var)**	IgG4 (non-complement fixing) Antibody to desmoglein-3 (component of desmosome connecting keratinocytes). Desmoglein-3, member of cadherin fam, links skin cells and other epithelial cells tightly to one another; effect adhesion in a calcium dep manner. This disease evolves more epitopes than the one that the original auto-ab bound to--epitope spreading. IgG4 can be spread in breastmilk so children born to mother w/ this will transiently show signs of this while breastfeeding. Beta chain of MHC II DRB1 subtype DRB1 0402 has negatively charged residue in peptide binding groove and is associated w/ PV. Tx: glucorticoids and immunosuppressives (cyclophasphamide--inferferes w/ DNA synth and stop cell div).
44	Celiac Dz (Celiac sprue/ Gluten sensitive enteropathy)	**Gluten Allergy; 90-95% have HLA-DQ2 and other express HLADQ8**	**relatives of person w/ it have higher chance of having it**	Gluten is a mix of proteins present in the grains of wheat, barley and rye. When it is degraded it releases a proline rich peptide (antigenic peptides) that survive transit through GI and arrives intact into small intestine. In subendothelial space peptide is deaminated by TTG (which incr its antigenicity)-->picked up and presented by APC to CD4 T cells--> that trigger immunologic process through TH1's and IFNg. Also peptide shown to trigger IL-15 from APC's which upreg MIC-A protein by endothelial cells (CD8 kill MIC-A exp cells-->intestinal damage) This leads to diarrhea, malabs, and ultimately nutritional def and failure to thrive. Kids usually present 6-24 mo w/ abd distension, diarrhea, malabs and weight loss, maybe anemia, muscular wasting. Tx immediately w/ corticosteroids. Most common presentation in adults is Iron def anemia that doesnt respond to oral therapy. Consider this dz in pts w/ unexplained bone fractures, transaminitis, or neurological sx including periph neuropathy, or ataxia as well as in women w/ infertility. Pt's w/ high risk of dev: DM type I, Downs, Turner, Willams sx, Autoimmuno thyroiditis, Selective IgA def. Histologically will see flattened mucosal surface, crypt hyperplasia and extensive inflamm infiltrate in celiac dz biopsy. Tx: Lifelong Avoidance of gluten. Dx: test IgA Ab against TTG. Pt having anti-TTG and anti-endomysial IgA= 100% predictive of celiac. Anti-gliadin IgG are less predictive (also found in IBD and healthy ppl). All suspected cases should be confirmed w/ bx. Oatmeal is not safe even though it doesnt have gluten b/c it can be cross-contaminated w/ gluten due to storage processes.
46	Hemolytic Disease of the Newborn	**Autoimmun against Rh Ag**		Rh antigen is not found in other tissues; only in RBCs. And it is widely spaced on blood cell surfaces. Because the Rh antigenic determinants are spaced very far apart on red cell surfaces, IgG antibodies to the Rh antigen do NOT fix complement and therefore do NOT hemolyze red blood cells in vivo The anemia of HDN due to Rhesus incompatibility is caused by removal of antibody-coated red cells by phagocytes.Rh antigen is not found in other tissues; only in RBCs. And it is widely spaced on blood cell surfaces. Because the Rh antigenic determinants are spaced very far apart on red cell surfaces, IgG antibodies to the Rh antigen do NOT fix complement and therefore do NOT hemolyze red blood cells in vitro. The direct Coombs test is used in the diagnosis of autoimmune diseases. It detects antibodies bound to the surface of red blood cells (Rh antigen). The red blood cells (RBCs) are washed (removing the patient's own serum) and then incubated with antihuman globulin (also known as "Coombs reagent"). If this produces agglutination of the RBCs, the direct Coombs test is positive. The indirect Coombs test is used in prenatal testing of pregnant women, AND in testing blood prior to a blood transfusion. It detects antibodies against RBCs that are present unbound in the patient's serum. In this case, serum is extracted from the blood, and the serum is incubated with RBCs of known antigenicity. If agglutination occurs, the indirect Coombs test is positive. Anti-Rh antibodies are IgG and can cross the placenta damaging fetal RBCs. (ABO Abs are IgM and are too large to cross the placenta) The anemia of HDN due to Rhesus incompatibility is caused by removal of antibody-coated red cells by phagocytes and that complement-mediated lysis does NOT occur. Alloimmunization and subsequent anti-Rhesus production by Rh-negative mothers can almost always be prevented by use of RhoGam (IgG anti-Rh [anti-D])) given at 28 weeks into pregnancy and just after birth (72 hours).

49	**Acute Systemic Anaphylaxis**	**Type I Hypersensitivity**	Hypersensitivity Reaction Type I to peanuts (see below). If mast cells in CT are activated can get anaphylaxis (hypersensitivity reaction in the blood stream). Give epinephrine (increased constriction of BV's SM but relation of airway's SM so it increases BP and airflow. Epinephrine acts at β2 Adrenergic receptors. RAST is used to determine which substances a person is allergic to.
50	**Allergic Asthma**	**Type I Hypersensitivity**	Hypersensitivity Reaction Type I. Person exposed to allergen-->allergen presented by APC to Th2--> Th2 release IL-4 and IL-5-->IL-5 recruits eosinophils & IL-4 causes B cells to isotype switch to IgE--> IgE binds to FceRI of mast cells (or basophils) and sensitizes--> subsequent exposure to allergen causes mast cells (or basophil) to degranulate and release histamine--> histamine increases vascular permeability, increases blood flow and increases SM contraction-->Narrowing of airways and trapping of air in lungs due to smooth muscle contraction in response to an allergen or physical stimulation of the environment (exercise, cold, etc.). Secondary asthmatic response follows the production of mediates like leukotrienes and prosteoglandins (these are produced during the inflammatory response occuring in asthma). Mucosal APC express high levels of costim B7.2 which also favors Th2. Wheal and flare response cells entering the extracellular space cause the wheal (rasied rash) and large amount of blood flow causes the flare. Atopy--predisposed to allergies but may not have them, Atropic--genetically predisposed to allergies and have them. Atopic ppl have genetic disposition to be Th2 dominant in responses to allergens. Immunotherapy--they try to desensitize the patients by subQ injection of high doses of allergen to promote a Th1 response (favors APCs that produce IL-12--TH0-->TH1 is by IL-12). Th1 makes IFN-g (prevents IgE) and leads to IgG not IgE. IgG inhibits mast cell and B cell activation.
51	**Atopic Dermatitis**	**Type I Hypersensitivity**	Hypersensitivity Reaction Type I. Increased IgE and impaired T-cell mediated immunity, esp. in skin. AD skin lesions are mostly Th2 CD4 cells and macrophages. Th2 cells secrete cytokines that inhibit Th1 cells. May be accounted for by a mutation in the FLG gene (filament aggragating protein fillagrin), which is an epidermal barrier protein. Increased susceptibility to severe viral skin infections, increased susceptibility to chronic funcal infection and decreased responsiveness to delayed type hypersensitivity skin testing. Susceptible to extensive herpesvirus infection due to inhibition of Th1 responses. Immunosuppressive drugs can be used to treat AD (reduce production of proinflamm. cytokines)
52	Drug-Induced Serum Sickness	**Type III Hypersensitivity**	Hypersensitivity Reaction Type III---due to immune complex formation from Ag and Ab. Occurs in the presence of excess antigen. When this occurs, antibody is not able to join and make larger, insoluble complexes, so the smaller ones get embedded in vascular walls. These IC activate complement via complement fixation of IgG antibodies, and C3a and C5a inflammatory mediators are produced which in turn can activate mast cells to release more inflammatory mediates.
53	Contact Sensitivity to Poison Ivy	**Type IV Hypersensitivity**	Hypersensitivity Reaction Type IV. Most common cause of this is through poison ivy but also can be from things like nickel ion. Poison ivy usually presents w/ a linear pattern of blisters called Hoebner phenomenon (rash only occurs in initial areas of contact. T cell mediated response in which haptens bind to self proteins and are taken up via macrophages and presented with MHC II to TH1 cells. It involves both Th1 and CTL responses in a sensitized person. Ag-specific cytotoxic CD 8+ T cells on target cells displaying the foreign Ag (Lipid-like haptens enter the cytosol of skin cells directly by diffusing through the plasma membrane and then bind to intracellular proteins. Proteins generated from the haptenated proteins in the cytosol are delivered to MHC class I molecules. Attacked by Ag-specific CD 8+ T cells that have become primed and activated on a PREVIOUS encounter with the Ag). In the TH1 and macrophage mediated, Ag in local tissues is processed by APCs & presented on MHC II. Ag-specific Th1 cells can recognize the Ag locally at the site of the injection, and release chemokines (e.g. CCL5) and cytokines (IFNg, TNFa, LT, IL-3, & GM-CSF) that recruit macrophages to site of Ag deposition. Ag presentation by newly recruited macro amplifies response. TNFa incr the expression of adhesion molecules on local BVs & increase vascular permeability (so greater homing of macrophages to skin in response to chemokines). Release of IL-3 and GM-CSF stimulates the production of macrophages. IFNg activates macrophages, increasing the release of inflammatory mediators. TNFa and LT (lymphotoxin) released by Th1 cells are involved in local tissue destruction. Other mediators released by TH1 cells such as stromelysin, degrade the proteins of the ECM which maintain the integrity of the skin. The inflammatory mediators also act on mast cells to cause degranulation and the release of histamine-->itching. Once sensitivity is acquired it is lifelong w/ shortened time between contact and rash w/ subsequent exposures. When a person contacts poison ivy pentadecacatechol penetrates skin--> antigenic peptides are presented b MHC II to TH1 cells--> TH1 activate macrophase-->which produce inflamm. Skin lesions are due to heavy infiltration of the contact sites w/ blood cells combined w/ localized destruction of skin cells. Tx: Corticosteroids (inhibit NFkB), antihistamines, patients are told to cut their fingernails. Use patch test to determine if ppl are allergic to something.